Preservation of cardiac function in Transient Receptor Potential V4 knockout mice after myocardial infarction measured by magnetic resonance imaging

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Introduction

The Transient Receptor Potential V4 (TRPV4), expressed in endothelium throughout the cardiovascular system, is a cation channel that contributes to intracellular Ca^{++} homeostasis and cell volume regulation.[1-3] Pharmacologic activation of TRPV4 has been associated with circulatory collapse and failure of the endothelial barrier.[4] In the present study, the effects of TRPV4 deletion ($TRPV4^{-/-}$) on cardiac function was examined in a myocardial infarction (MI) model.

Methods

One week post-MI (permanent ligation), scans were performed using a 9.4T vertical small bore magnet (Bruker, Billerica, MA). Four groups of mice (control groups n=4; wildtype (WT) with MI n= 12; $TRPV4^{-/-}$ with MI n=8) were induced and maintained under isoflurane (1-2%) anesthesia in medical air while respiration was continually monitored via a pillow sensor positioned under the abdomen (SA Instruments, Stoney Brook, NY). Fast gradient-echo scout images were acquired in three orthogonal planes covering the heart (TR/TE=137/2.7 ms, 128X128 matrix, FOV=6.0 cm, NEX=4) to determine the long axis of the left ventricle. Transverse, bright-blood, fast gradient-echo cine images (TR/TE=6.82/1.8 ms, 128X128 matrix, FOV=6.0 cm, 300 reps, 10 movie frames) were acquired in a single plane through the short axis of the left ventricle and were reconstructed using IntraGate (Bruker) retrospective cardiac gating software. Left ventricular end diastolic volume (EDV), left ventricular end systolic volume (ESV) and ejection fraction (EF) were calculated from cardiac function images. Upon completion of MRI, animals were sacrificed and lung wet weights and tibia lengths were recorded In a separate cohort of mice (n=4 both groups), area at risk and infarct size were measured after 30 min ischemia and 24 h reperfusion to determine any infarct differences between strains.

Results

End diastolic images are shown in Figure 1 in a wildtype control mouse (A) and a wildtype mouse one week post MI (B). The thinning of the infracted ventricle wall is clear in image B along with chamber dilation. There was no difference in cardiac function in the control groups (Fig 2A). Post-MI, EF was significantly greater in the $TRPV4^{-/-}$ mice (26±1% WT vs. 35±4% $TRPV4^{-/-}$, $P<0.05$). The ESV was significantly greater in WT mice (75.76±3.86µl WT vs. 54±95µl $TRPV4^{-/-}$, $P<0.05$) along with a non-significant increase in EDV (102.11±4.29µl WT vs. 80.45µl $TRPV4^{-/-}$, n.s.). Cardiac function and lung congestion were significantly correlated ($r=-0.73$, $P<0.01$, Fig 2B). From the ischemia reperfusion results, no difference in area at risk (47±6% WT vs. 48±3% TRPV4-/-, n.s.) or infarct size (56±4% WT vs. 56±6% TRPV4-/-, n.s.) was found between the two strains.

Discussion

MRI revealed preservation of cardiac function in the $TRPV4^{-/-}$ mouse 1 week post-MI. One potential explanation for the preserved ejection fraction in the $TRPV4^{-/-}$ mice would be different basal function between the two strains. To explore this possibility two groups of age-matched control mice, with no ligation, were imaged in the same manner as the infarct mice. There was no difference in cardiac measurements between groups of control animals; therefore any difference in cardiac function between strains after MI was not due to baseline function. In addition to basal function, another potential explanation for the post-MI results would be vascular differences between the strains. To examine potential vascular effects between the two strains, a cohort of mice underwent ischemia/reperfusion, and area at risk and infarct size was measured. There was also no difference between stains in area at risk or infarct size after ischemia/reperfusion. These results indicate that TRPV4 deletion produces a cardio-protective phenotype and suggests an important relationship between the endothelium and cardiac function.

References

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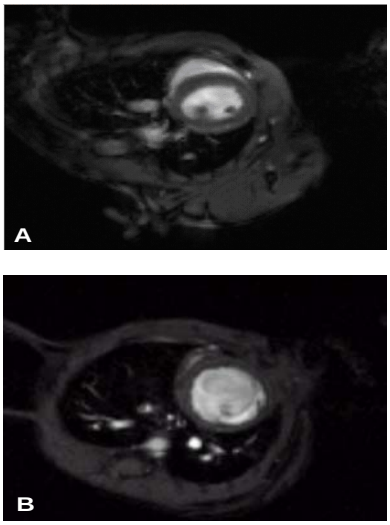

Figure 1. True-transverse short axis images of A) control and B) 1-week post-MI wildtype mice.

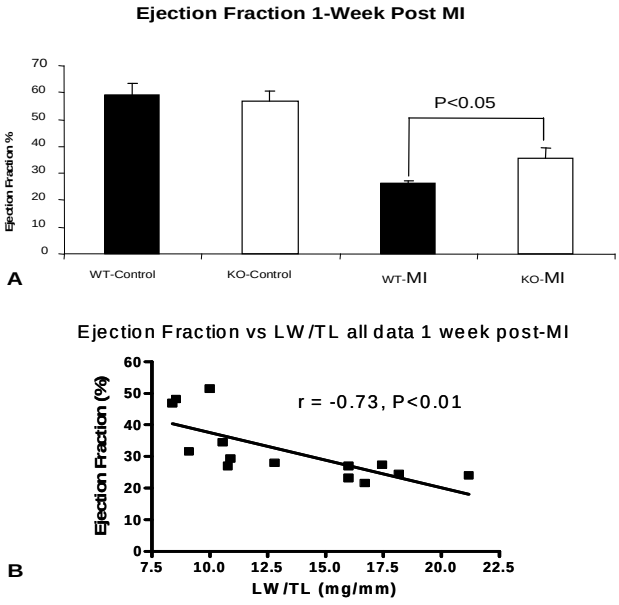

Figure 2. A) Significant preservation of cardiac function in TRPV4-/- vs. wildtype mice 1-week post-MI. B) Ejection Fraction is significantly correlated to lung weight normalized to tibia length.